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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	16

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/965,522	LAL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on th cover sheet with th corresp nd nc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12,30-45,56 and 58-60* is/are pending in the application.

4a) Of the above claim(s) *1,12,30,33,35,36,39,44,45 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,31,32,34,37,38,40-43 and 58-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 1, 11, 12, 30-45, 56, and 58-60 are pending in the instant application.

[2] Applicant's amendment to the specification, amendment to claims 11, 37, and 40, and addition of claims 57-59 (renumbered as claims 58-60 – see item 6 below) in Paper No. 13, filed April 11, 2003, is acknowledged.

[3] Receipt of an Information Disclosure Statement filed as Paper No. 14 is acknowledged.

[4] Claims 1, 12, 30, 33, 35, 36, 39, 44, 45, and 56 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

[5] Claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 are being examined on the merits.

[6] The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claims 57-59 have been renumbered as claims 58-60 as claim 57 has already been presented in the application as originally filed and subsequently cancelled in Paper No. 4.

[7] Applicant's arguments in Paper No. 13 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[9] Claim 40 is objected to as there is a period at the end of part (a). It is suggested that, for example, applicant delete the period at the end of part (a).

Claim Rejections - 35 USC § 101

[10] The rejection of claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 under 35 U.S.C. 101 because the claimed invention lacks patentable utility is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 4 of Paper No. 9). Applicant argues (beginning at page 3 of Paper No. 13) the claimed invention has a specific utility based on the homology to human renal sodium phosphate transport protein (NPT1) and the known function of NPT1, which is transport of phosphate ions across cellular membranes. Applicant argues that homology to sequences of known function is a commonly used and allegedly reliable technique in the art for elucidating function. Applicant cites Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) as allegedly providing evidence that sequence identity between polypeptides has been found to be a reliable threshold for determining homology. (It is noted that the examiner has interpreted applicant's argument as meaning sequence identity has been found to be a reliable threshold for determining *functional* homology). Applicant argues that the amino acid sequence of SEQ ID NO:1 shares 48% identity over 402 amino acids with the amino acid sequence of NPT1, thus exceeding the reliability threshold of Brenner et al. for determining functional homology. Applicant argues the polypeptide of SEQ ID NO:1 also has a similar hydrophobicity plot to NPT1 and shares potential N-glycosylation sites at two amino acids of NPT1. Based on this asserted evidence, applicant argues that SEQ ID NO:1 has a specific utility as a transporter of phosphate ions. Applicants' arguments are not found persuasive.

It is noted that applicant improperly attempts to apply the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) to the asserted 48 % identity between SEQ ID NO:1 and NPT1. Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that their comparisons "have been assessed using proteins whose relationships are known reliably from their structures and functions, as described in the

SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized*, i.e., functionally characterized by empirical laboratory experiments and structurally characterized by generating a three-dimensional structure of the proteins (see for example Murzin et al. *J Mol Biol* 247:536-540). In the instant case, the function of SEQ ID NO:1 has not been empirically determined nor has the three-dimensional structure been solved for comparison with NPT1. The function of SEQ ID NO:1 has been assigned solely on the basis of a relatively low sequence identity to NPT1. Thus, an ordinarily skilled artisan would recognize that the teachings of Brenner et al. do not apply to a functional assignment of NAPTR based solely on 48 % sequence homology to NPT1. Instead, Brenner has expressed his views on functional annotation of a protein based solely on sequence analysis in a manuscript titled "Errors in Genome Annotation" (*Trends Genetics* 15:132-133). In this reference, Brenner (*Trends Genetics* 15:132-133) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph) and describes the errors that are inherent in predicting function based on sequence identity. For example, Brenner (*Trends Genetics* 15:132-133) states, "[w]ithout laboratory experiments to verify the computational methods and their expert analysis, it is impossible to know for certain [whether the function assigned to a protein by annotation is correct]" (page 132, left column, second paragraph). While the polypeptide encoded by SEQ ID NO:2 may share more than 48 % sequence identity with NPT1, this is no indication that the polypeptide encoded by SEQ ID NO:2 shares the same function as NPT1. It is well known in the art that structural identity is not necesssarily predictive of functional similarity. Addressing applicant's statement that sequence identity shared between two proteins is reliable technique in the art for elucidating function, one of ordinary skill in the art would recognize that, while sequence identity between two polypeptides can be used to *predict* function, empirical analysis is the only true method of determining a protein's function with a reasonable reliability. As a specific example, Scott et al. (*Nat Genet* 21:440-443) teach a polypeptide that has 45 % sequence identity (similar to the 48% identity shared between SEQ ID NO:1 and NPT1) with a human sulfate transporter and that, based on structural homology has been proposed to function as a sulfate transporter (page 440, left column, abstract). However, an empirical analysis of the protein measuring its

ability to transport various ions revealed the protein is actually a chloride-iodide transport protein (page 441, left column, third full paragraph). Scott et al. "conclude that pendrin does not function as a sulfate transporter, as suggested by its close homology to other sulfate transporters, but instead functions as a sodium-independent transporter of chloride and iodide. These results underscore the importance of confirming the function of newly identified gene products even when database searches reveal significant homology to proteins of known function" (page 441, left column, third full paragraph). Thus, a skilled artisan would recognize that the function of a polypeptide cannot be assigned based solely on sequence identity, and would conclude that the specification has *not* established with a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1 or belongs to the class of phosphate cotransporters. Also, while SEQ ID NO:1 and NPT1 may all share *potential* N-glycosylation sites, an ordinarily skilled artisan would recognize that nearly all full-length proteins exhibit *potential* N-glycosylation sites and therefore, would not be a factor in a determination of whether SEQ ID NO:1 and NPT1 share the same function. Furthermore, while SEQ ID NO:1 and NPT1 may have rather similar hydrophobicity plots, such plots have been shown to be similar even among proteins with relatively low sequence homology that exhibit different functions. For example, Vrljic et al. (*J Mol Microbiol Biotechnol* 1:327-336) analyze the hydrophobicities of three proteins that function in the transport of different molecules (page 329, Figure 2) revealing strikingly similar hydrophobicity plots. Thus, based on the cited references, an ordinarily skilled artisan would recognize that a protein's function *cannot* be assigned based on structural identity alone. Thus, one of ordinary skill in the art would not recognize with a reasonable probability that the polypeptide of SEQ ID NO:1 encoded by SEQ ID NO:2 has utility similar to NPT1.

Even if the specification provided sufficient evidence to convince an ordinarily skilled artisan of a reasonable probability that the polypeptide of SEQ ID NO:1 shares the same function as NPT1, which it does not, one of ordinary skill in the art would recognize that polypeptides with similar function do not necessarily have similar utilities. For example, even if overexpression of NPT1 was found to be indicative of a particular disease (which it is not), this would provide no indication that overexpression of SEQ ID

NO:1 would similarly be predictive of the same or any other disease as further experimentation would be required to make this determination. Furthermore, even if polypeptides with similar function were found to have similar utilities – which, in the instant case they do not – the examiner knows of no well-established utility for NPT1 that could be applied to the polypeptide of SEQ ID NO:1.

Applicant argues (beginning at the top of page 5 of the specification) the claimed invention has many specific utilities disclosed in the specification such as being used in diagnostic assays, as antagonists or inhibitors, or as a delivery mechanism for targeting an agent to cells or tissues. Applicant cites diseases that are allegedly associated with decreased expression of SEQ ID NO:1 and others that are associated with increased expression of SEQ ID NO:1. Applicant argues these utilities are specific and define a "real world" use for the claimed invention. Applicant's arguments are not found persuasive.

With regard to use of the claimed antibody for diagnosis of disease or as an antagonist or inhibitor, in order for an antibody to be useful, as asserted, for diagnosis of a disease or as an antagonist or inhibitor, there must be a well-established or disclosed correlation or relationship between the claimed antibody and a disease or disorder. The presence of a protein or encoding polynucleotide in tissue that is derived from brain tumor cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified and related in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many polypeptides and encoding polynucleotides are expressed at equal levels and in identical forms in both normal *and* diseased tissues. Therefore, one necessarily needs to know, e.g., that SEQ ID NO:1 is either present only in brain tumor tissue to the exclusion of normal tissue or is expressed in higher levels in brain tumor tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed antibody as a diagnostic for disease(s). In this case, additional experimentation is required in order to determine the relationship between SEQ ID NO:1 and a *specific* disease state. The specification merely provides a "laundry list" of diseases that are *associated* with increased or decreased

expression of SEQ ID NO:1. There is no indication of what this association may be or how such association may be exploited for disease diagnosis or treatment. In the absence of any disclosed relationship between SEQ ID NO:1 and any *specific* disease or disorder and the lack of any correlation between SEQ ID NO:1 with any known disease or disorder, any information obtained from an ELISA expression analysis would only serve only as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101. Therefore, for the reasons of record and the reasons stated above, the claimed antibody has no specific and substantial asserted utility.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The enablement rejection of claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated in item 9 above. The rejection was fully explained in a previous Office action (see item 7 of Paper No. 9). Applicant essentially presents the same arguments as stated in item 9 above. Applicant additionally cites Bonneau et al. (*J Struc Biol* 134 :186-190) as evidence in asserting that homology to sequences of known function is a common and allegedly reliable technique in the art for elucidating function. Applicant's arguments are not found persuasive for the reasons set forth in item 9 above. As with the teachings of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078), applicant improperly attempts to apply the teachings of Bonneau et al. (*J Struc Biol* 134 :186-190) in asserting that homology to sequences of known function is a common and allegedly reliable technique in the art for elucidating function. The reference of Bonneau et al. (*J Struc Biol* 134 :186-190) addresses functional inferences based on three dimensional structural predictions. As the function of SEQ ID NO:1 has been inferred solely from its primary structure (amino acid sequence) and its relationship to NPT1 and not its predicted three dimensional structure, the teachings of Bonneau et al. (*J Struc Biol* 134 :186-190) clearly do not apply here. Therefore, since the claimed invention is not

supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

[12] The written description rejection of claims 11, 31, 32, 34, 42, 43, and 58 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 8 of Paper No. 9). Applicant argues (beginning at the bottom of page 7 of Paper No. 13) the rejection has been overcome by amendment. Applicant's argument is not found persuasive. It is noted that claim 11 recites "a polypeptide *comprising* the amino acid sequence of SEQ ID NO:1" (italics added for emphasis). A variety of polypeptides may comprise the amino acid sequence of SEQ ID NO:1, e.g., fusion proteins. Such proteins can elicit antibodies that do not bind the polypeptide of SEQ ID NO:1 and would instead bind epitopes found within other portions (i.e., non-SEQ ID NO:1 amino acid sequence) of a polypeptide comprising or having SEQ ID NO:1. Thus, the claimed genus of antibodies encompasses species that are widely variant with the ability to bind *any* polypeptide comprising SEQ ID NO:1, encompassing species of antibodies that bind proteins that have not been disclosed in the specification. The single representative species of an antibody that binds the polypeptide of SEQ ID NO:1 fails to represent all species of antibodies that bind all polypeptides comprising SEQ ID NO:1. As such, the specification contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

[13] The scope of enablement rejection of claims 11, 31, 32, 34, 42, 43, and 58 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 9 of Paper No. 9). Applicant argues (page 7 of Paper No. 13) the rejection is overcome by amendment. Applicant's argument is not found persuasive. The specification, while being enabling for an antibody that binds the polypeptide of SEQ ID NO:1, does not reasonably provide enablement for an antibody that binds *any* polypeptide *comprising* SEQ ID NO:1. The scope of the claimed antibody is not commensurate in scope with the enablement provided by the specification. It is the examiner's position that, based on the broad scope of claimed antibodies, undue

experimentation would be required for a skilled artisan to make and use all antibodies that bind to any polypeptide *comprising* SEQ ID NO:1, which encompasses antibodies that bind polypeptides other than the amino acid sequence of SEQ ID NO:1. The specification fails to provide guidance for using those antibodies that bind those polypeptides other than SEQ ID NO:1 that are part of a protein *comprising* SEQ ID NO:1. Furthermore, it is highly unpredictable that an antibody generated against proteins *comprising* SEQ ID NO:1 will necessarily have the ability to bind that portion of the protein having the sequence of SEQ ID NO:1. Regarding claim 58, even if the antibody were limited to an antibody that binds to a polypeptide *consisting* of SEQ ID NO:1, there is no indication in the specification or the prior art that such an antibody would have the ability to inhibit transport of phosphate ions. The specification provides no indication of the region or regions of SEQ ID NO:1 involved in phosphate transport that would enable a skilled artisan to make an antibody with the ability to inhibit phosphate ion transport – if at all possible. As such, undue experimentation would be required to make and use all antibodies that bind a protein *comprising* SEQ ID NO:1.

Thus, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102 and 35 USC § 103

[14] In view of applicant's amendment to limit the claims to limit the antibody to an antibody that specifically binds to a polypeptide comprising or consisting of SEQ ID NO:1, the rejection of claims 11, 32, 34, 37, 38, 40, and 41 under 35 U.S.C. 102(e) as being anticipated by Feder et al. (IDS reference; US Patent 5,872,237) is withdrawn. The antibody of Feder et al. is generated from a polypeptide that

comprises an amino acid sequence that is identical only to amino acids 1-11, 13-94, 96-159, and 161-401 of SEQ ID NO:1. Thus, Feder et al. does not anticipate the claimed invention.

[15] In view of applicant's amendment to limit the claims to limit the antibody to an antibody that specifically binds to a polypeptide comprising or consisting of SEQ ID NO:1, the rejection of claims 11, 32, 37, and 38 under 35 U.S.C. 102(b) as being anticipated by Dillner et al. (WO 91/18294) is withdrawn. The antibody of Dillner et al. is generated from a 20 amino acid peptide, wherein only amino acids 11-17 of the peptide of Dillner are 100 % identical to SEQ ID NO:1. Thus, Dillner et al. does not anticipate the claimed invention.

[16] The rejection of claims 31, 42, and 43 under 35 U.S.C. 103(a) as being unpatentable over Feder et al. in view of Krebber et al. (US Patent 5,514,548) is withdrawn. Feder et al. do not anticipate the invention as stated above and Krebber et al. do not remedy the deficiency of Feder et al. Thus, the claimed invention is not rendered obvious by the combination of Feder et al. and Krebber et al.

[17] The rejection of claims 31, 34, and 40-43 under 35 U.S.C. 103(a) as being unpatentable over Dillner et al. in view of Krebber et al. is withdrawn. Dillner et al. do not anticipate the invention as stated above and Krebber et al. do not remedy the deficiency of Dillner et al. Thus, the claimed invention is not rendered obvious by the combination of Dillner et al. and Krebber et al.

Conclusion

[18] Status of claims:

- Claims 1, 11, 12, 30-45, 56, and 58-60 are pending.
- Claims 1, 12, 30, 33, 35, 36, 39, 44, 45, and 56 are withdrawn from consideration.
- Claims 11, 31, 32, 34, 37, 38, 40-43, and 58-60 are rejected.
- No claim is in condition for allowance.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date

of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

REBECCA E. PRUTY
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GROUP ~~1900~~ 1600